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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,598	03/08/2002	Jose Cibelli	60141.0068USU1	1067

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,598	CIBELLI, JOSE	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,22,23 and 25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,22,23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03/08/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply filed 10/12/2005 has been received. Claims 7-21,24 and 28-72 have been cancelled. Claims 1,3,22 and 25-27 have been amended. Claims 1-6,22,23 and 25-27 are pending and under consideration in the instant office action.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6,22,23 and 25-27 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's arguments have been fully considered and are not persuasive as set forth below. The rejection is maintained for reasons of record set forth at pages 3-11 of the office action dated 04/12/2005.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The claims are drawn to a method of making a nuclear transfer embryo that is incapable of differentiating into a particular lineage by isolating a mammalian differentiated fibroblast cell, genetically engineering said cell by knocking out a gene required for differentiation into a particular lineage, and transferring the nucleus from the genetically engineered cell into a recipient cell to form a nuclear transfer embryo. Claim 1 is drawn to two different scenarios wherein in one case, the recipient and donor (fibroblast) are of the same species while in the other case, the differentiated donor cell (fibroblast) is human and the recipient oocyte is rabbit or bovine. The claims are now limited to use of a fibroblast as a donor and an oocyte as a recipient. Claims 25-27 limit the gene being knocked out to specific genes or sets of genes.

The specification provides only prophetic teachings with respect to the claimed methods. The specification prophetically discusses disruption of a gene in differentiated somatic cells wherein the gene is necessary for development of a particular lineage followed by transfer of the nucleus into donor cells. The specification does not provide any working examples or any guidance with respect to what cell types to use as donors, to what cell types to use as recipients

or what genes, when knocked out, would be effective in accomplishing the claimed invention. Applicant has limited the claims with respect to donor and recipient cell type and claims 25-27 are limited to knockout of specific genes. However, the other pending claims are generic. Paragraph 0043 of the specification purports that any gene expressed specifically in a specific lineage can be knocked out to cause "de-differentiation" of the respective lineage. The specification lists a number of examples of such genes but fails to provide any guidance as to what the genes do or what effect the gene knockout, if any, will have. The specification fails to provide any guidance, whatsoever, as to how to genetically engineer any gene at all so as to prevent formation of a particular lineage.

1) The first aspect of the rejection is based on the failure of the specification to teach what genes are to be knocked out to inhibit the development of a particular lineage (see pages 5-6 of the office action dated 04/12/2005). It would be highly unpredictable what effects any particular gene knockout would have on lineage development in a resultant NT embryo and whether any particular gene knockout would arrive in a lineage deficient embryo as claimed.

Applicant argues that experimentation would not be undue to determine what genes, when knocked out, would lead to an embryo incapable of differentiating into a particular cell lineage (see page 13, paragraph 2). Applicant argues that one of skill in the art would be able to figure out exactly what genes to pick as the relevant tools were readily available to make such a determination.

In response, Applicant has not provided any means of choosing a gene in such a way as to overcome the unpredictability known in the art as set forth at pages 5-6 of the office action dated 04/12/2005. Applicant has not provided any criteria for selecting such genes and has not

set forth any information such that one of skill in the art could predict without undue experimentation whether any single particular gene would be useful. The phenotypic effect of tradition gene knockout is highly unpredictable even when gene function is known. How knockout of a gene would affect dedifferentiation and subsequent development in a nuclear transfer embryo is highly unpredictable even to those of highest skill in the art. Therefore, Applicant's argument is not persuasive. It would require undue experimentation to determine what genes, when knocked out, would lead to a lineage-deficient nuclear transfer embryo.

2) The second aspect of the rejection relates to the breadth of the claims with respect to donor cell type. Claim 1 has been limited to fibroblast cells. However, this limitation is insufficient in overcoming this aspect of the rejection because not all species of fibroblasts have been shown in the art to be successful in nuclear transfer, particularly after genetic modification. Furthermore, the teachings in the specification are merely prophetic and fail to overcome the underdeveloped nature of the state of the art. For example, as set froth at page 7 of the office action dated 04/12/2005, human dermal fibroblasts do not proliferate under regular culture conditions and would not be useful in the claimed methods (see page 7 of the office action dated 04/12/2005). Furthermore, a comparison of separate Black Welsh sheep primary cell fibroblast cultures showed vast differences in the number of doublings prior to senescence; 110 doublings versus 40 doublings (Denning, page 224, col. 2, lines 16-19). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (Denning, page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Thus, the ability to genetically engineering even fibroblast cells is unpredictable from species to

species and cell line to cell line (see page 7 of the office action dated 04/12/2005). Thus, limiting the claims to fibroblasts of any species is not sufficient to overcome this aspect of the instant rejection.

3) The third aspect of the rejection is based on the breadth of the claims with respect to the type of recipient cell used in the claimed method. Applicant has limited the scope of the recipient cell to an oocyte, which is sufficient to overcome only this aspect of the rejection.

4) The fourth aspect of the rejection is based on the stage of the oocyte used as a recipient (see pages 9-10 of the office action dated 04/12/2005). Applicant has failed to address this aspect of the rejection and it is, therefore, maintained for reasons of record.

5) The fifth aspect of the rejection relates to cross species nuclear transfer (page10-411 of the office action dated 04/12/2005). Claim 1 has been limited to either single-species nuclear transfer or transfer of a human nucleus into a rabbit or bovine oocyte. Applicant has referred to the specification at page 20, paragraph 41, which teaches that transfer of a human nucleus into a rabbit or bovine oocyte is known in the art. These references, PCT US00/05434 and PCT US 00/12631 teach transfer of a human epithelial cell nucleus into a bovine oocyte, which yielded only one structure having greater than 16 cells that formed a colony with ES cell-like morphology. No characteristics were shown for the cells to show they were human or were ES-like other than the ES-like morphology (see US00/12631, pages 49-50). PCT US00/05434 additionally taught a similar result by transplant of a human keratinocyte into a bovine oocyte (page 40). Neither application taught use of a fibroblast or genetic engineering of the somatic cell prior to transfer. In light of the state of the art with respect to the nuclear donor cell type used in genetic engineering (see pages 5-8 of the office action dated 04/12/2005) and the lack of

characterization of the human/bovine chimeras of the art mentioned by Applicant, Applicant's argument that cross-species nuclear transfer is enabled by the prior art does not overcome the rejection of the instant claims. It is noted that neither '434 nor '631 teach a rabbit species as a recipient cell.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claims 3,22,24 and 51 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicant's amendments to the claims. A new grounds of rejection necessitated by Applicant's claim amendments is set forth below.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites the limitation "the cells" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The previous rejection of claim 51 and of claim 24 under 35 USC 102(b) is withdrawn in light of Applicant's cancellation of the claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

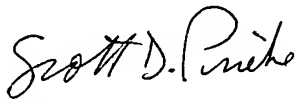
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632



SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER